REMARKS

Claims 1-9 remain in the present application. Claims 1-4 have been withdrawn from consideration as non-elected claims. Claims 5-9 are pending and claim 5 is herewith amended.

Support for any amendments to the claims can be found throughout the specification and claims as originally filed. No new matter has been added.

Any amendments to the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

The Applicant is appreciative of the opportunity for the Applicant's Attorney to conduct a telephone interview with the Examiners Wegert and Kemerer on August 12, 2003. Amendments to claim 5 that might place the claims in condition for allowance were discussed. Also discussed were ways that the Deth Declaration could be strengthened and resubmitted.

Claim Rejection - 35 U.S.C. §112, First Paragraph

Claims 5-9 are rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The Examiner states that while the specification is enabling for a method of "identifying therapeutic agents for neuropsychiatric diseases involving the D4 receptor and in which phospholipid methylation has been shown to be affected, does not reasonably provide enablement for agents or processes involving other neuropsychiatric diseases in which a clear link from the D4 receptor to phospholipid methylation has not been established."

Applicant respectfully traverses the foregoing rejection.

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The presently claimed application is directed to a method of identifying a therapeutic process or agent for treating schizophrenia or a related neuropsychiatric disorder involving the dopamine D4 receptor. The method includes using a cultured cell line that naturally expresses D4 receptors or transfected with the D4 receptor gene and determining the level of phospholipid methylation upon administration of candidate therapeutic process or agent to cells and making a determination of the phospholipid methylation in the cells. An increase in the level of phospholipid methylation indicates that the agent is potentially therapeutically effective for treating schizophrenia or related neuropsychiatric disorders.

Applicant submits that at the time of the filing of the application, those of ordinary skill in the art would have known from the published literature that neuropsychiatric disorders other than schizophrenia involved dopamine D4 receptor-mediated phospholipid methylation. Applicant provides herein a Declaration under 37 C.F.R. §1.132 by Dr. Richard C. Deth as a supplement to this response. The Deth Declaration supports the inference that an ordinary skilled artisan would reasonably believe based on the specification and on common knowledge that there is a sufficient link between phospholipid methylation and the dopamine D4 receptor in neuropsychiatric disorders other than schizophrenia that the method of the invention would apply.

As described in the Deth Declaration, exemplary neuropsychiatric disorders where dopamine D4 receptor-mediated phospholipid methylation is involved include, for example, autism, attention-deficit hyperactivity disorder and Alzheimer's disease. Autism can effect adenosylsuccinate lyase (ASL) enzyme in the purine synthesis pathway by genetic mutations. As explained, such

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impairment causes single-carbon groups from the folate pathway to be preferentially diverted toward purine synthesis, resulting in a deficit in the availability of methyl THF for folate-dependent methylation of homocysteine or for folate-dependent methylation of the dopamine D4 receptor (D4R). (*See* Deth Declaration, Paragraph 7.) Such ASL mutations impair D4R-mediated phospholipid methylation and impair other methylation reactions such as DNA methylation. Here, as the Deth Declaration states, the published literature shows that there is a link between autism and D4R-mediated phospholipid methylation.

Another exemplary neuropsychiatric disorder is attention-deficit hyperactivity disorder (ADHD). ADHD is a widely known disorder in dopamine signaling. D4R is also known to be linked to ADHD (*see* Deth Declaration, ¶9). Therefore, it is reasonable to conclude that dopamine D4 receptor-mediated phospholipid methylation is related to ADHD.

Another exemplary neuropsychiatric disorder is Alzheimer's disease. As explained in Deth Declaration, ¶10, Alzheimer's disease is associated with reduced levels of vitamin B-12 which is the required co-factor for methionine synthase that brings methyl groups from the folate pathway to the D4 dopamine receptor. The enzyme activity of methionine adenosyltransferase, required in the cycle of D4 dopamine receptor-mediated PLM, is also reduced in Alzheimer's disease. Here, again, a link has been shown associating a "related" neuropsychiatric disorder and D4R-mediated phospholipid methylation.

Based on the foregoing descriptions of exemplary neuropsychiatric disorders and their relationship to dopamine D4 receptor-mediated phospholipid methylation, Applicant believes that the specification in combination with common knowledge has

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been shown to be enabling for neuropsychiatric disorders other than schizophrenia. Undue experimentation will, therefore, not be required.

Accordingly, Applicant respectfully requests reconsideration and withdrawal of the foregoing rejection.

CONCLUSION

In view of the foregoing amendments and remarks, Applicant believes that the present application is in condition for allowance.

The Examiner is encouraged to telephone the undersigned attorney to discuss any matter that would expedite allowance of the present application.

Respectfully submitted,

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application	:	Richard C. Deth
Application No.	:	09/550,103
Filed	:	April 14, 2000
Confirmation No.	:	8235
For	:	METHODS OF IDENTIFYING AND DETERMINING THE EFFECTIVENESS OF THERAPEUTIC PROCESSES OR AGENTS FOR THE DIAGNOSIS AND TREATMENT OF SCHIZOPHRENIA AND RELATED DISORDERS
Examiner	:	Sandra Wegert
Attorney's Docket	:	NU-431AX

#13
RJ
9/24/03

TC Art Unit: 1647

* *

I hereby certify that this correspondence is being sent via facsimile to Examiner Sandra L. Wegert, TC Art Unit 1647, Fax No. (703) 308-4242, on Sept. 22, 2003.

By: Holliday C. Heine
Holliday C. Heine, Ph.D.
Registration No. 34,346
Attorney for Applicant(s)

* *

DECLARATION OF RICHARD C. DETH, PH.D.
UNDER 37 C.F.R. §1.132

Via Facsimile
After Final
Commissioner for Patents
Washington, D.C. 20231

I, Richard C. Deth, Ph.D., a citizen of the United States of America, residing at 1484 Beacon Street, Waban, Massachusetts 02468, declare the following:

1. I received my doctoral degree in Pharmacology from the University of Miami (Florida) in 1975. I am currently a Professor of Pharmacology at Northeastern University in Boston, Massachusetts.

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2. I specialize in the study of signaling pathways involving G protein-coupled receptors such as the D_4 dopamine receptor. My particular interest is focused on folate-dependent methylation reactions, their control by dopamine and growth factors, and their involvement in various mental illnesses.

3. I am an inventor of the subject matter set forth in the present, above-identified patent application.

4. I have read and am familiar with the prosecution history of the present application, including the Office Action dated May 20, 2003 (Paper No. 12).

5. The detailed action of the Office Action rejects claims 5-9 under 35 U.S.C. §112, first paragraph, because "the Specification, while being enabling for a method identifying therapeutic agents for neuropsychiatric diseases involving the D_4 receptor and in which phospholipid methylation has been shown to be affected, does not reasonably provide enablement for agents or processes involving other neuropsychiatric diseases in which a clear link from the D_4 receptor to phospholipid methylation has not been established."

6. This declaration provides support that the specification is enabling for methods of identifying agents or processes for treating neuropsychiatric disorders, in addition to schizophrenia, in which there is a link from the dopamine D_4 receptor to phospholipid methylation. Specifically, given the theory behind the methods of the invention as proposed by the Applicant and described in the specification and given the state of general

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knowledge at the time the instant application was filed concerning the likely causes of other neuropsychiatric diseases related to schizophrenia, those of ordinary skill in the art would have believed that the Applicant's experimental showings with respect to schizophrenia were directly relatable to other neuropsychiatric diseases. Herein below are descriptions of exemplary neuropsychiatric disorders or diseases involving changes in D_4 receptor-linked phospholipid methylation.

7. An exemplary neuropsychiatric disorder is autism. From what was known about the causes of autism at the time this application was filed, it is my opinion that one of ordinary skill in the art would accept my assertion that the methods of the invention would be useful in identifying agents or processes for treating autism. Autism can be caused by genetic mutations (such as those impairing the adenosylsuccinate lyase enzyme in the purine synthesis pathway[1,2]) that result in the diversion of single-carbon groups away from the folate pathway. As I have now shown, this type of diversion results in a deficit in the availability of 5-methyl tetrahydrofolate for folate-dependent methylation of the dopamine D_4 receptor and subsequent D_4 receptor-mediated phospholipid methylation. Thus, it would be considered credible by those of ordinary skill that detection of a change in the level of dopamine D_4 receptor-mediated phospholipid methylation could be used as an assay system for candidate agents for the treatment of autism, as claimed in the instant application.

8. Adenosylsuccinate lyase mutations, as discussed above, cause preferential diversion of single-carbon groups from the

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folate pathway to purine synthesis. It is known that another developmental disorder, Lesch-Nyhan syndrome is also associated with excessive activity of the purine synthesis pathway[3]. Additional developmental disorders, including Fragile-X syndrome[4] and Angelman and Prader-Willi Syndromes[4], involve abnormal DNA methylation and gene silencing. Thus, developmental disorders as a group appear to involve abnormal folate-dependent methylation events, linking them to folate-dependent D_4 receptor-linked phospholipid methylation and to use of the assay system according to the invention as a screening tool for candidate therapeutic agents.

9. One of the hallmark symptoms of autism is impaired attention. This includes attention to other persons as well as impairment of attention-related learning[5]. This symptom is also common in schizophrenia[6] and, of course, attention-deficit hyperactivity disorder (ADHD). D_4 dopamine receptors have been linked to the risk of ADHD[7] and ADHD is widely recognized as a disorder of dopamine signaling [8], so diseases in which there is a deficit of attention are likely to be related to D_4 receptor-mediated phospholipid methylation. Thus, attention-deficit hyperactivity disorder can be considered as being a "schizophrenia-related disorder," since both disorders appear to include an important role for D_4 dopamine receptor-mediated phospholipid methylation.

10. Alzheimer's disease is associated with reduced levels of vitamin B-12[9,10], the required co-factor for methionine synthase that brings methyl groups from the folate pathway to the D_4 dopamine receptor. Treatment with 5-methyl tetrahydrofolate, the

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source of methyl groups for the D_4 receptor phospholipid methylation process, has been shown to improve dementia [11]. Levels of S-adenosylmethionine, a methyl donor, are lower in Alzheimer's disease[12]. Furthermore, the enzyme activity of methionine adenosyltransferase, required in the cycle of D_4 dopamine receptor-mediated phospholipid methylation, is reduced in Alzheimer's disease[13]. Thus, there is considerable evidence for impairments that involve D_4 receptor-mediated phospholipid methylation in Alzheimer's disease, such that it should also be considered as a "related neuropsychiatric disorder" in the context of the screening methods of the invention as claimed in the instant application.

11. Based on the foregoing and what is generally known in the art, those of ordinary skill would believe from what I have disclosed in the instant application that there is a sufficient correlation between changes in D_4 receptor-linked phospholipid methylation and other neuropsychiatric disorders related to schizophrenia that the screening methods claimed therein would be likely to generate candidate therapeutic agents or processes for these related disorders. The state of the art at the time of filing, when read with the knowledge of my results, indicates to those of ordinary skill that neuropsychiatric disorders related to schizophrenia, in general, involve changes in dopamine D_4 receptor-linked phospholipid methylation.

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I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the Unites States Code, and that such willful false statements so made may jeopardize the validity of the document, or application, or any patent issuing thereon.

Signed this _____ day of _____, 2003.

By: _____
Richard C. Deth, Ph.D.

Enclosure: *List of Cited References (Attached hereto)*

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